Cell

The Clammy Grip of Parasitic Tumors

Robin A. Weiss[1,*] and Ariberto Fassati[1]
[1]Wohl Virion Centre, Division of Infection and Immunity, University College London, Gower Street, London WC1E 6BT, UK
*Correspondence: r.weiss@ucl.ac.uk
http://dx.doi.org/10.1016/j.cell.2015.03.034

An epidemic of leukemia among bivalve molluscs is spreading along the Atlantic coast of North America, with a serious population decline of soft-shelled clams. In this issue of *Cell*, Metzger et al. use forensic DNA markers to demonstrate that the leukemia cells have a clonal origin and appear to be transmitted through sea water.

Those of us who have enjoyed clam bakes on the beach at Cold Spring Harbor Laboratory may soon find that this mode of networking among scientists has become a thing of the past. The soft-shelled clam (*Mya arenaria*) is suffering a population dive owing to the spread of a lethal leukemia-like cell. Similar leukemias have been observed in other species of edible bivalve molluscs such as mussels, cockles, and oysters that are farmed along the Atlantic littoral of North America. The disease in soft-shelled clams now ranges from Chesapeake Bay to the Canadian province of Prince Edward Island 1,500 km to the northeast. Importation of clam stocks by shellfish farmers may have exacerbated its spread.

Steve Goff's laboratory at Columbia University, working with ecologists at Environment Canada, had previously identified a retrotransposon in the clams called *Steamer*, which is greatly amplified in the leukemic cells (Arriagada et al., 2014). Using genetic analysis of *Steamer* integration sites, mitochondrial single-nucleotide polymorphisms, and microsatellite variation, they now show that the leukemia has a monoclonal origin sharing common alleles that are different from their hosts (Metzger et al., 2015). In this respect, the leukemia in clams is similar to the Devil facial tumor disease (DFTD) of the marsupial carnivore, the Tasmanian devil, whose survival is endangered by rapidly spreading infection of a clonal neuro-endocrine cancer (Pearse and Swift, 2006, Murchison et al., 2012), and to canine transmissible venereal tumor (CTVT), which has a worldwide distribution in dogs (Murgia et al., 2006; Murchison et al., 2014).

DFTD is spread by biting, whereas CTVT, as its name implies, is sexually transmitted. The mode of transmission of the clam leukemia is not yet firmly established, but it is likely that these filter feeders take up tumor cells from the seawater through their siphons (Figure 1) and that the cells then parasitize the new host. When the leukemic clone of clams first emerged is unknown, but since the disease was noted in the late 1970s, it must be at last 40 years old. DFTD was first recorded in Tasmanian devils in 1996 (Pearse and Swift 2006), whereas the venereal tumor in dogs is estimated to date from an ancient breed like the husky some 11,000 years ago (Murchison et al., 2014). Of course, even a 10,000 year period is a snapshot on the evolutionary timescale of the hosts, and one can speculate how many other cases of tumor cells evolving into parasites may have occurred in species that may now be extinct.

In addition to the three naturally occurring transmissible tumors of clams, dogs, and devils, there are several case histories of human malignancy arising from occult tumor cells in donor organ or tissue transplants that then emerge in the immunosuppressed transplant recipient (Murgia et al., 2006; Siddle and Kaufman, 2015). There are also cases of transplacental tumor transmission from mother to child and between twins in utero. Among inbred strains of laboratory rodents, there would be an opportunity for tumor cells to spread from one individual to another without crossing a major histocompatibility (MHC) barrier. However, only one example has been documented—that of leukemia in a colony of Syrian hamsters at NIH 50 years ago; the leukemic cells could even be transmitted by mosquitoes (Banfield et al., 1965), presumably by passive transfer on the mouth parts rather than by undergoing a replication cycle in the insect host.

How do transmissible tumors manage to overcome histocompatibility barriers? It appears that there are a variety of mechanisms, including downregulation of class I and class II MHC genes and secretion of immunosuppressive cytokines (Belov, 2012; Siddle and Kaufman, 2015). In CTVT, there is a fine balance between progressive disease without an anti-tumor immune response and regression when allograft rejection kicks in. In DTFD, the tumor is relentlessly progressive. Both CTVT and DFTD have close to homozygous MHC class I alleles, and their initial emergence may have been facilitated by a relatively inbred host population with limited MHC diversity. Invertebrates like clams do not have as sophisticated a tissue recognition system as the MHC of higher vertebrates, yet certain cell surface molecules help to distinguish between self and non-self. However, non-malignant somatic cell invasion and even germ cell parasitism has been documented in marine invertebrates such as colonial tunicates (Rinkevich, 2011). Metzger et al. (2015) suggest that the lack of an MHC system may make molluscs more susceptible than vertebrates to transmissible tumors. As CTVT is the only known transmissible cancer that can regress, understanding what triggers rejection may be key to inducing regression of other transmissible tumors and perhaps non-transmissible cancers too.

As Metzger et al. (2015) document in their Introduction, leukemia occurs not only in soft-shelled clams, but also in other bivalve molluscs in the same region of North America. This observation raises the question of whether the

Figure 1. A Bowl of Soft-Shelled Clams, *Mya arenaria*, with Extended Siphons
Courtesy of the Department for Natural Resources, State of Maryland.

tumors in other species represent cross-species infections from *Mya arenaria* or whether each host species has evolved its own transmissible tumor. CTVT is known to be readily transplantable experimentally to other canid species and even to foxes (Murgia et al., 2006; Belov, 2012), and it will be easy to determine the species of origin of transmissible leukemias in other bivalves. If each tumor is species specific, what environmental factors may have facilitated their independent emergence around the same time and place?

How might transmissible tumors be contained to reduce the threat to their host species? CTVT in dogs has spread to all five continents, but it is self-limiting and presents no danger to the host species as a whole. In India, the high incidence of CTVT in street dogs has been diminished in some cities by castration. To save the Tasmanian devil from extinction, a possible tumor vaccine is being explored as well as containment of healthy animals on islands and on peninsulas with barrier fences to keep out affected devils (Belov, 2012). For the soft-shelled clam, it will be important to be vigilant to stop importation of clams from affected areas to currently unaffected ones like Florida.

In the meantime, it is safe for humans to eat clams, even raw oysters. Enjoy them while you can!

REFERENCES

Arriagada, G., Metzger, M.J., Muttray, A.F., Sherry, J., Reinisch, C., Street, C., Lipkin, W.I., and Goff, S.P. (2014). Proc. Natl. Acad. Sci. USA *111*, 14175–14180.

Banfield, W.G., Woke, P.A., Mackay, C.M., and Cooper, H.L. (1965). Science *148*, 1239–1240.

Belov, K. (2012). BioEssays *34*, 285–292.

Metzger, M.J., Reinisch, C., Sherry, J., and Goff, S.P. (2015). Cell *161*, this issue, 255–263.

Murchison, E.P., Schulz-Trieglaff, O.B., Ning, Z., Alexandrov, L.B., Bauer, M.J., Fu, B., Hims, M., Ding, Z., Ivakhno, S., Stewart, C., et al. (2012). Cell *148*, 780–791.

Murchison, E.P., Wedge, D.C., Alexandrov, L.B., Fu, B., Martincorena, I., Ning, Z., Tubio, J.M., Werner, E.I., Allen, J., De Nardi, A.B., et al. (2014). Science *343*, 437–440.

Murgia, C., Pritchard, J.K., Kim, S.Y., Fassati, A., and Weiss, R.A. (2006). Cell *126*, 477–487.

Pearse, A.M., and Swift, K. (2006). Nature *439*, 549.

Rinkevich, B. (2011). Chimerism *2*, 1–5.

Siddle, H.V., and Kaufman, J. (2015). Immunology *144*, 11–20.